

COPY FOR IB

PATENT COOPERATION TREATY

PCT

REC'D 28 JAN 2005

WIPO
REPORT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-E2158	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/KR2002/001775	International filing date (day/month/year) 18 SEPTEMBER 2002 (18.09.2002)	Priority date (day/month/year)
International Patent Classification (IPC) or national classification and IPC IPC7 C07D 307/32		
Applicant SK CORPORATION et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 24 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14 APRIL 2004 (14.04.2004)	Date of completion of this report 06 JANUARY 2005 (06.01.2005)
Name and mailing address of the IPEA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, Hee Jin  Telephone No. 82-42-481-5412

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/KR2002/001775

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages 1-2 , as originally filed
pages 3-19 , filed with the demand
pages _____, filed with the letter of _____
- ☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under Article 19
pages 20-22/2 , filed with the demand
pages _____, filed with the letter of _____
- ☒ the drawings:
pages 1/1 , as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language; all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language English which is

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☒ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed," and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION

International application No.

PCT/KR2002/001775

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 1-16	YES
	Claims	NO
Inventive step (IS)	Claims 1-16	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-16	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The amendments filed 14.04.2004 are not considered to introduce the subject matter which extends beyond the content of the application as filed. Consequently, this examination report is done based on the amendments.

Reference is made to the following documents:

D1 : WO 02/10147 A1

D2 : US 6355848 B1

1. Novelty

The present invention relates to a process for the production of optically pure (S)- β -hydroxy- γ -butyrolactone in a continuous manner by catalytic and regiospecific hydrogenation of ester group closest to the hydroxy group of an optically active 2-hydroxy substituted succinic acid ester in the presence of the metal-impregnated support catalyst system.

D1 discloses a process for the production of (S)- β -hydroxy- γ -butyrolactone through the hydrogenation of 2-hydroxy substituted succinic acid ester.

D2 discloses a process for the preparation of (S)-1,2,4-butanetriol from (S)-malic acid by hydrogenation in the presence of a metal catalyst.

Although the process of D1 is the same as that of the present invention in starting material, product, catalyst system and reaction condition, the present invention employs an organic or inorganic acid, differently from D1.

D2 does not disclose the same catalyst system and reaction condition as those of the present invention.

Therefore, the present invention is considered to be novel under PCT Article 33(2).

2. Inventive Step

D1 is considered to represent the most relevant state of the art and differs only in the presence of acid.

Addition of an acid improves unexpectedly the optical purity (ee>99.0%), which is not obvious from the prior art.

(Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/KR2002/001775

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

Therefore, the present invention is considered to involve an inventive step under PCT Article 33(3).

3. Industrial applicability

The present invention is considered to be industrially applicable under PCT Article 33(4).

of large quantities of waste, and thus is difficult to apply industrially.

In U.S. Pat. No. 6,221,639 there is disclosed a method for the production of (S)- β -hydroxy- γ -butyrolactone having high optical purity, comprising reacting amylopectin using an enzyme to afford an oligosaccharide which is then reacted with an alkaline
5 anionic exchange resin and an oxidizing agent, to obtain (S)-3,4-dihydroxy-butyric acid, which is desorbed and subjected to esterification and cyclization. However, this method is disadvantageous in terms of low preparation yield due to a complexity of the reaction mechanism, and high cost is problematic when applied on the large scale.

As stated above, the conventional preparation methods adopt a batch type
10 process using a solid or liquid reagent such as an oxidizing agent or a reducing agent, which makes the production efficiency unfavorable. In particular, a large quantity of waste is generated during the process and a complexity of the process is a major cause of low preparation yield. Accordingly, such methods are unsuitable for the preparation of a large scale and are limited in their industrial applications.

15

DISCLOSURE OF THE INVENTION

Leading to the present invention, the intensive and thorough research into continuous production processes of (S)- β -hydroxy- γ -butyrolactone, carried out by the present inventors aiming to solve the problems encountered in the prior arts, led to the development of a catalyst capable of being easily prepared and increasing production
20 efficiency of the target product, by which a production yield can be increased, and to the development of a reaction system capable of retaining a desired optical purity.

Therefore, it is an object of the present invention to provide a continuous process for efficiently producing chemically pure (S)- β -hydroxy- γ -butyrolactone while

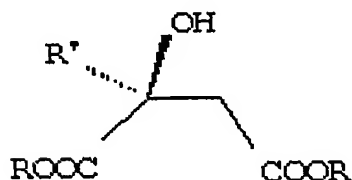
retaining an optical activity to a desired level from optically pure carboxylic acid ester derivative employed as a starting material, by which the simplicity of the process and the environmental safety can be assured.

In accordance with an embodiment of the present invention, there is provided
 5 a continuous process for the production of chemically pure (S)- β -hydroxy- γ -butyrolactone having desired optical activity, which comprises:

a) dissolving carboxylic acid ester derivative having the following Formula 2 in solvent at an amount of 2-50 wt%, the solvent being added with an organic or inorganic acid;

10

Formula 2

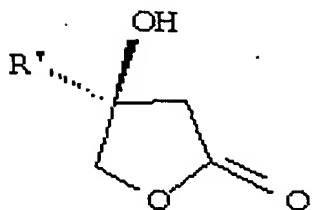


15

b) subjecting the carboxylic acid ester derivative solution to hydrogenation at 50-500 °C under a pressure of 15-5,500 psig at weight-hourly-space-velocity of 0.1-10 h⁻¹, in a fixed bed reactor charged with a metal catalyst-impregnated inorganic oxide support, a molar ratio of hydrogen to carboxylic acid ester derivative ranging from 2 to 10; and

c) recovering (S)- β -hydroxy- γ -butyrolactone having the following Formula 4 from the hydrogenation products,

Formula 4

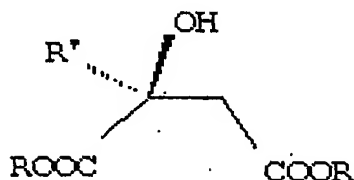


wherein R represents linear or cyclic alkyls, or aryl groups, of from 1 to 10 carbon atoms, and R' represents hydrogen or methyl.

In accordance with a preferred embodiment of the present invention, there is provided a continuous process for the production of chemically pure (S)- β -hydroxy- γ -butyrolactone having desired optical activity, which comprises:

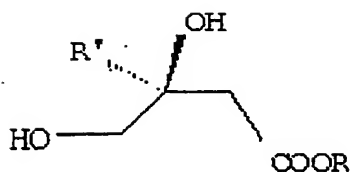
a) dissolving carboxylic acid ester derivative having the following Formula 2 in solvent at an amount of 2-50 wt%, the solvent being added with an organic or inorganic acid;

Formula 2

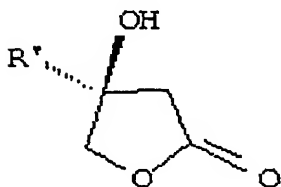


b) subjecting the carboxylic acid ester derivative solution to hydrogenation at 50-500 °C under a pressure of 15-5,500 psig at weight-hourly-space-velocity of 0.1-10 h⁻¹, in a fixed bed reactor charged with a metal catalyst-impregnated inorganic oxide support to give hydrogenation products containing an intermediate having the following Formula 3 and (S)- β -hydroxy- γ -butyrolactone having the following Formula 4, a molar ratio of hydrogen to carboxylic acid ester derivative ranging from 2 to 10; and

Formula 3



Formula 4



- c) subjecting the hydrogenation products to cyclization in the presence of a solid acid catalyst, whereby the intermediate present therein is converted into (S)-β-hydroxy-γ-butyrolactone; and
- d) recovering said (S)-β-hydroxy-γ-butyrolactone from the resulting products, wherein R represents linear or cyclic alkyls, or aryl groups, of from 1 to 10 carbon atoms, and R' represents hydrogen or methyl.

10

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph showing an optical purity of (S)-β-hydroxy-γ-butyrolactone prepared by hydrogenating carboxylic acid ester derivative according to the present invention, measured with gas chromatography (GC) (Example 11).

15

BEST MODES FOR CARRYING OUT THE INVENTION

According to the present invention, optically pure (S)-β-hydroxy-γ-butyrolactone is continuously produced through hydrogenation of carboxylic acid

ester derivative while continuously passing it through a fixed bed reactor charged with a catalyst comprising a metal-impregnated support. This process is advantageous in that higher yield of a target product can be achieved while retaining the optical purity to a desired level, and in that regeneration and continuous use of catalyst are assured.

5 Further, it is not required to perform a complicated post-treatment step such as removal of the catalyst using a filter.

The present continuous process for the production of (S)- β -hydroxy- γ -butyrolactone is represented in the following Reaction Scheme 1. Carboxylic acid 1 is converted in the presence of a solid acid catalyst into carboxylic acid ester derivative 2, which is then dissolved in a solvent added with an organic or inorganic acid. The solution is fed to a fixed bed reactor, and the carboxylic acid ester derivative 2 contained therein is subjected to hydrogenating in the presence of a catalyst having a metal component highly dispersed on an inorganic oxide support. As a result, (S)- β -hydroxy- γ -butyrolactone 4, a target product, may be directly

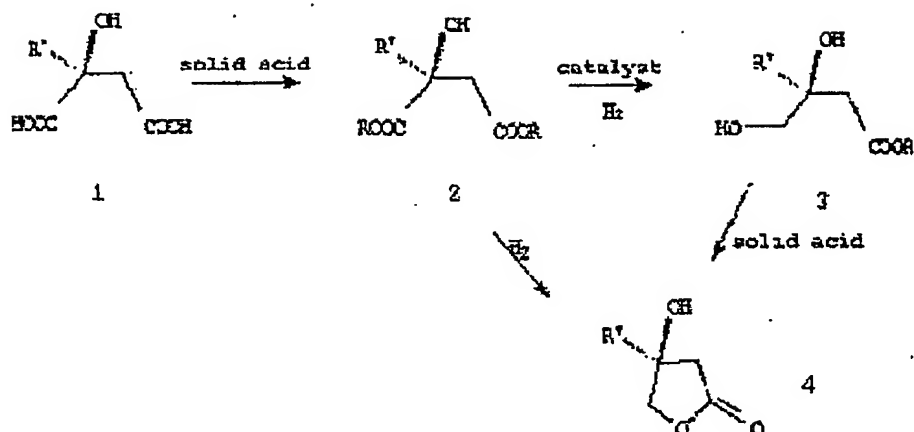
10 produced, or a reaction intermediate such as methyl-di-hydroxy- γ -butyric acid ester 3 may be formed. At the same time, the carboxylic acid ester derivative 2, which is a reactant, may be partly hydrolyzed and converted into carboxylic acid 1 again.

After hydrogenation, such a re-formed carboxylic acid 1, which is present in the resulting reaction products, may be removed through esterification by use of

20 alcohol in the presence of an acid catalyst. In addition, the reaction intermediate such as methyl-di-hydroxy- γ -butyric acid ester 3 may be converted into optically pure (S)- β -hydroxy- γ -butyrolactone 4 through cyclization reaction without performing separation in advance. Hereinafter, the term "carboxylic acid ester derivative 2" is used in the way of including substituted carboxylic acid ester compound, substituted

25 carboxylic acid ester derivative, or substituted carboxylic acid ester.

Reaction Scheme 1



wherein R represents linear or cyclic alkyls, or aryl groups; of from 1 to 10
5 carbon atoms, and R' represents hydrogen or methyl.

The metal component in the hydrogenation catalyst suitable in the present
invention may be selected from the group consisting of nickel (Ni), palladium (Pd),
platinum (Pt), rhodium (Rh), iridium (Ir), ruthenium (Ru), osmium (Os), and
10 combinations thereof. As a support, use can be made of alumina, silica, silica-
alumina, zirconia, titania, zeolite or a molecular sieve.

The carboxylic acid ester derivative 2, which is used for the preparation of
optically pure (S)-β-hydroxy-γ-butyrolactone as a starting material, is obtained
through esterification of the carboxylic acid with an alcohol that is exemplified by
15 linear alcohols, such as methyl alcohol, ethyl alcohol, n-propyl alcohol, etc., cyclic or
aromatic alcohols, having 1-10 carbon atoms. The alcohol component is preferably
used at an amount of 2-40 equivalents based on the carboxylic acid 1. In the solid

acid catalyst, the esterification is preferably performed at 50-150 °C under a pressure of 1-300 psig at weight-hourly-space-velocity (WHSV) of 0.1-10 h⁻¹. As such, the solid acid catalyst is preferably a sulfonate-substituted resin having strong acidity. Further, L-malic acid or L-citramalic acid may be used as the carboxylic acid 1.

5 If the reaction is carried out beyond the above conditions, a yield of the carboxylic acid ester derivative 2 may be decreased and the deactivation rate of the catalyst is increased, thus lowering the advantages of a continuous production.

The hydrogenation of the carboxylic acid ester derivative 2 for the production of the substituted γ -butyrolactone is performed at 50-500 °C under a hydrogen partial
10 pressure of 15-5,500 psig at weight-hourly-space-velocity (WHSV) of 0.1-10 h⁻¹, and preferably, at 60-250 °C under 1,000-5,000 psig at WHSV of 0.2-10 h⁻¹, and more preferably, at 60-200 °C under 1,200-4,500 psig at WHSV of 0.2-6 h⁻¹.

If the reaction is conducted outside of the above conditions, a production yield of the substituted γ -butyrolactone product is decreased or the deactivation rate of the
15 catalyst is increased, thus losing the advantages of a continuous production.

In order to completely convert the carboxylic acid ester derivative 2 by hydrogenation, a molar ratio of hydrogen to carboxylic acid ester derivative should be 1.0 or higher. However, in consideration of economic benefit of the process, such a molar ratio is preferably adjusted in the range of from 2 to 10. As such, the non-
20 reacted hydrogen, which passes through the reactor, is re-compressed and circulated to the reactor. Depending on the reaction conditions, the target product may be directly recovered from the resulting reaction mixture through separation. Alternatively, in order to further increase the conversion rate, the resulting reaction products may be re-circulated to the reactor, and then the target product is recovered through separation.

25 In the hydrogenation, it is required to use a specific solvent to conduct a

conversion of the carboxylic acid ester derivative 2 retaining its optical activity. In this regard, the solvent should be capable of dissolving the carboxylic acid ester derivative having high viscosity to smoothly supply such carboxylic acid ester derivative to the reactor. In addition, the solvent is responsible for easy removal of
5 reaction heat generated during the subsequent hydrogenation (and esterification), and should not react with the reactants including the carboxylic acid ester derivative 2 and hydrogen.

In consideration of the above, the solvent required for the hydrogenation is selected from the group consisting of methyl alcohol, ethyl alcohol, n-propyl alcohol,
10 isopropyl alcohol, dioxane, γ -butyrolactone, tetrahydrofuran, water, and combinations thereof. It is preferred that the carboxylic acid ester derivative in the solvent has a concentration of 2-50 wt%.

Meanwhile, according to the prior art literatures regarding oxidative dehydrogenation, it is reported that oxidation (dehydrogenation) does not occur under
15 a strong acidic condition (Coord. Chem. Rev. 1999, 187, 121). However, the carboxylic acid ester derivative used in the present invention contains a secondary alcohol moiety therein, and thus during hydrogenation by metal catalyst, partial racemization occurs by oxidation (dehydrogenation) and reduction (hydrogenation) of the secondary alcohol moiety, thereby decreasing optical purity. With the aim of
20 overcoming the problems related to racemization, an acid is introduced to the solvent as an additive. In producing (S)- β -hydroxy- γ -butyrolactone having high optical purity (ee>99.0%), there has not been reported such employment of the acid for the hydrogenation of the carboxylic acid ester derivative from any prior art literatures.

That is, the optical purity of an initial product can be increased in a continuous
25 hydrogenation process by adding an organic or inorganic acid additive to the solvent

as aforementioned. Such an acid is selected from the group consisting of formic acid, oxalic acid, DL-malic acid, acetic acid, nitric acid, sulfuric acid, phosphoric acid, hydrochloric acid, and combinations thereof. Among them, formic acid, oxalic acid or nitric acid is preferably used. The acid is used at an amount of 0.1-50 wt%, and
5 preferably at an amount of 0.1-20 wt%, based on the solvent weight. Further, the acid may be previously diluted in water to have a desired degree of acidity. If the amount of the acid falls out of the above range, the optical purity of the substituted γ -butyrolactone product is decreased, and the deactivation rate of the catalyst is increased by impurities (e.g., sulfur) contained in the acid additive.

10 The catalyst used in hydrogenation is used in the form of metal-impregnated support, in which the usable metal is exemplified by nickel (Ni), palladium (Pd), platinum (Pt), rhodium (Rh), iridium (Ir), ruthenium (Ru), osmium (Os), and combinations thereof. Among them, ruthenium is most preferable. For the preparation of the catalyst, a metal precursor in the form of chlorides, nitrides or acetyl
15 acetates thereof may be used. In order to properly control a concentration and a degree of dispersion of the used metal, chlorides and acetyl acetates are most preferable. As the support, suitable is inorganic oxides such as alumina, silica, silica-alumina, zirconia, titania, zeolite or a molecular sieve. In particular, silica is most preferable. Silica useful as the support is 100 m²/g or more, and preferably 200-600
20 m²/g in a surface area measured by BET method of nitrogen adsorption, to increase a degree of dispersion of the metal.

The degree of dispersion of the metal onto the support ranges from 2 to 50%, and more preferably from 2 to 25%. If the degree is less than 2%, catalytic activity is decreased. On the contrary, the degree exceeding 50% leads to decrease of optical
25 purity.

The shapes of the support particulates include, but are not limited to, circular, cylindrical, and granular forms. For exhibiting suitable mechanical properties, the support formed to the circular or cylindrical shape is preferably used.

The metal in the catalyst is used at an amount of 0.1-15 wt%, and more preferably, 0.5-10 wt%. When the amount is less than 0.1 wt%, activity for hydrogenation is decreased as well as selectivity. On the other hand, when the amount exceeds 15 wt%, a process cost becomes higher due to use of expensive metals. The metal is impregnated onto the support by any conventional method such as incipient wetness impregnation, excess water impregnation, spraying or physical mixing. After impregnating the metal onto the support, calcination is conducted for 2 hours or more under an air or an inert gas atmosphere. As such, a calcination temperature should be within the range of 300-700 °C, and more preferably 300-600 °C. If the calcining temperature is lower than 300 °C, the precursor decomposition of the metal upon impregnation may become insufficient, thus resulting in incomplete calcination. Meanwhile, if the temperature is higher than 600 °C, satisfactory catalytic performance may not be exhibited due to low degree of dispersion of the metal.

After the calcined catalyst is charged into the fixed bed reactor, the catalyst is preferably reduced by hydrogen. As such, the reduction may be performed at 50-500 °C for at least 2 hours, depending on kinds of the impregnated metal.

As mentioned above, the present invention is directed to the continuous production process of optically pure substituted γ -butyrolactone with a high yield, in which the hydrogenation of carboxylic acid ester derivative compound 2 is conducted in the presence of the catalyst system of the metal-impregnated support. This process is advantageous in terms of higher yield of the target product due to adopting

continuous reaction by use of a fixed bed reactor, economic benefit due to use of easily regenerable catalyst, and simplicity of the recovery process requiring no removal step of the catalyst with a filter.

In the present invention, the fixed bed reaction system is adopted to perform
5 the process as described above. Although the fixed bed reaction system is not limited to specific reactor types or addition and flowing directions of reactants, it is preferable to use a trickle-bed type reactor equipped with an apparatus capable of uniformly dispersing hydrocarbons and hydrogen as the reactants in the whole reaction system while the reactants flow from the upper portion to the lower portion in
10 the reactor so as to smoothly come in contact with the reactants.

The resulting reaction mixture discharged from the reactor flows to a solvent recovery apparatus, in which at least a portion of the solvent is separated from the reaction product. For example, the solvent recovery can be accomplished by a distillation tower and a flash vaporizer. The product or concentrated material
15 discharged from the lower portion of the solvent recovery apparatus is transferred to a vacuum distillation apparatus.

According to the present invention, an improved catalyst is employed for the production of (S)- β -hydroxy- γ -butyrolactone. Reaction yield and productivity may be increased by use of such a catalyst. Moreover, introduction of the inorganic or
20 organic acid additive results in production of (S)- β -hydroxy- γ -butyrolactone having excellent optical purity by a continuous hydrogenation process.

A better understanding of the present invention may be obtained in light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention.

EXAMPLE 1

Preparation of Catalyst

To a 500 cc flask, secondary distilled water and then 18 g of ruthenium chloride (RuCl_2) were introduced, yielding an aqueous ruthenium chloride solution. Circular silica 100 g (1/8") was added to a rotatable metal impregnation container equipped with a motor capable of controlling a rotational speed, and then the ruthenium solution was uniformly dispersed to the silica while the container was rotated. Even after addition of the ruthenium solution was terminated, the motor was further rotated at the same rotational speed for about 60 minutes. Then, the ruthenium-impregnated silica was transferred to a muffle furnace and calcined at 500 °C for 3 hours under an air atmosphere. The content of ruthenium in the sintered catalyst, measured by X-ray fluorescence analysis, was 3.0 wt%.

EXAMPLE 2

Continuous Preparation of Dimethyl (S)-malate

25 g of a solid acid catalyst was charged into an automated high pressure fixed bed reactor made of 316 stainless steel, and then purged with nitrogen gas. Thereafter, the temperature in the reactor was raised from room temperature to 105 °C and the reaction pressure was maintained at 100 psig. Then, L-malic acid was dissolved in 8 equivalents of methyl alcohol, and was introduced into the reactor at WHSV 4.0 h⁻¹, yielding a reaction product with a conversion efficiency of 93%, a reaction selectivity of 98% and a yield of 91%.

The resulting reaction mixture by the continuous manner as above was distilled under reduced pressure, to obtain dimethyl (S)-malate having purity of 99.8%, optical purity of 99.9% or more and an isolation yield of 90%. This product might be afforded even by a batch type reaction requiring a reaction time period of 2-4 hours.

5

EXAMPLES 3-6

Continuous Preparation of (S)- β -hydroxy- γ -butyrolactone

10 g of the catalyst prepared by the method of Example 1 was charged into a continuous high pressure reactor made of 316 stainless steel. After the temperature in the reactor was raised to 350 °C at a rate of 2 °C/minute, the catalyst was reduced under
10 a hydrogen atmosphere for 6 hours, and then the reactor cooled to room temperature was purged with nitrogen gas. While the temperature in the reactor was raised from room temperature to a reaction temperature at a rate of 1 °C/minute, hydrogen of 100 sccm was introduced thereto. The amount of the introduced hydrogen was twice the amount required for reaction, and dimethyl-(S)-malate was dissolved in water added
15 with an acid additive. The reactant solution having 20 wt% of dimethyl (S)-malate was fed to the reactor and hydrogenated at 95-125 °C under a hydrogen pressure of 3,380 psig at WHSV 1.5 h⁻¹. In case of using water containing an acid additive (*), a desired optical purity was confirmed at the initial reaction stage (6 hour after the reaction was initiated). The results are shown in Table 1, below. In case of using
20 water not added with an acid, it was not until 50 hours later that ee value of 99% or more was obtained. The reaction product was analyzed with a FID (flame ionization detector) after gas chromatography (30m×0.25mm×0.25m HP-5 column), and ee value

thereof was measured by gas chromatography (30m×0.25mm×0.25m beta-DEX column).

TABLE 1

Ex.No.	Solvent System	Reaction Temp.(°C)	Time ²⁾	Conversion (%)	Selectivity ¹⁾ , (%)	ee (%)
3	Water+A*	110	6	77.2	89.2	99.29
4	Water+B*	110	7	75.4	90.2	99.27
5	Water+C*	115	5	70.2	92.2	99.25
6	Water	110	6	75.4	77.9	98.12

Note: 1) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)-β-hydroxy-γ-butyrolactone; and

2) Time period from the beginning of the reaction to the collection of the sample

A*: formic acid, B*: oxalic acid, C*: nitric acid.

EXAMPLES 7-10

In hydrogenation of dimethyl (S)-malate using the solvent such as alcohol or water mixed with 2% formic acid additive, the higher optical purity was assured in a water than in alcohol. These examples were carried out in the manner set forth in Example 3 under the conditions of temperature of 100-135 °C, hydrogen pressure of 3,380 psig and WHSV 1.5 h⁻¹. The used solvent and the reaction results are given in the following Table 2.

TABLE 2

Ex.No. ¹⁾	Temp. (°C)	Solvent	Conversion (%)	Selectivity ²⁾ (%)	ee (%)
7	120	H ₂ O	79.2	88.1	99.19
8	125	MeOH	83.0	84.9	98.25

9	125	EtOH	85.7	84.1	97.52
10	125	IPA	95.2	43.5	96.12

Note: 1) catalyst : Example 1; and

2) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)- β -hydroxy- γ -butyrolactone.

EXAMPLES 11-13

5 Continuous Preparation of (S)- β -hydroxy- γ -butyrolactone

Hydrogenation of dimethyl (S)-malate was carried out in the manner set forth in Example 3 under the conditions of temperature of 110 °C, hydrogen pressure of 3,380 psig and WHSV 0.5-1.5 h⁻¹, varying with kinds of the catalyst, in the water solvent system added with formic acid. In the following Table 3, the results show the influence of the degree of dispersion of the metal in terms of the production efficiency. The degree of dispersion, measured with chemical adsorption of carbon monoxide, refers to a value calculated from the equation (molecules of carbon monoxide adsorbed to a metal atom \times 100). As shown in Table 3, when the degree of dispersion is increased, a space-time yield is drastically increased with maintenance of ee value.

15

TABLE 3

Ex.No.	Catalyst System	Dispersion (%)	WHSV (h ⁻¹)	Conversion (%)	Selectivity ¹⁾ (%)	ee (%)
11	Ru/SiO ₂ -A	18	1.5	79.4	82.3	99.36
12	Ru/SiO ₂ -B	4.0	1.0	76.5	82.5	99.20
13	Ru/SiO ₂ -C	1.0	0.5	85.4	84.2	99.18

Note: 1) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)- β -hydroxy- γ -butyrolactone.

20

EXAMPLE 14

Hydrogenation of dimethyl (S)-malate was carried out in the manner set forth in Example 3 under the conditions of temperature of 100 °C, and WHSV 1.5 h⁻¹ in the presence of Ru/SiO₂-A catalyst employed in Example 11 using a water solvent system added with formic acid. The reaction results varying with the applied hydrogen pressure are given in the following Table 4.

TABLE 4

Pressure (psig)	Conversion (%)	Selectivity ¹⁾ (%)	ee (%)
2,483	65.1	85.2	99.19
3,380	74.0	83.0	99.36

Note: 1) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)-β-hydroxy-γ-butyrolactone.

EXAMPLES 15-22

Hydrogenation of dimethyl (S)-malate was carried out in the manner set forth in Example 3. At this time, the solvent and reaction conditions were variously changed without use of the acid additive. When the acid additive was not used, the optical purity was lowered, compared with the case of using the acid additive. The reaction results are given in the following Table 5.

TABLE 5

Ex.No. ¹⁾	Solvent	Temp. (°C)	WHSV (h ⁻¹)	Conversion (%)	Selectivity ²⁾ (%)	ee (%)
15	MeOH	120	0.5	75.2	85.6	98.10
16	MeOH	135	0.5	84.2	78.4	97.56
17	H ₂ O	120	1.0	74.2	79.3	98.15

18	H ₂ O	135	1.0	84.0	75.5	97.25
19	IPA	135	0.25	97.2	42.1	95.32
20	THF	130	0.5	75.6	84.0	97.23
21	EtOH	125	0.5	86.1	55.2	96.52
22	EtOH	125	1.0	79.8	64.6	97.12

Note: 1) catalyst: Example 1

2) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)- β -hydroxy- γ -butyrolactone.

EXAMPLE 23

5 Continuous Reaction of (S)- β -hydroxy- γ -butyrolactone for Long-term Period

Using the catalyst prepared in Example 1, a continuous reaction was carried out in a reactor similar to that illustrated in Example 3 for a long-term period. Even though the reaction was carried out for 600 hours or more, no deactivation of the catalyst was observed. Such results are presented in Table 6, below.

10

TABLE 6

Reaction Time	100 hr	200 hr	600 hr
Conversion (%)	75.2	74.1	73.9
Selectivity ¹⁾ (%)	83.5	84.2	85.2
Optical Purity (%)	99.17	99.21	99.23

Note: 1) Selectivity refers to the sum of respective selectivity for methyl-di-hydroxy-butyric acid ester as a reaction intermediate and (S)- β -hydroxy- γ -butyrolactone.

15

EXAMPLE 24

Production and Isolation of (S)- β -hydroxy- γ -butyrolactone

Using 50 g of the catalyst prepared in Example 1, the hydrogenation reaction was carried out in a reactor similar to that illustrated in Example 3. During the reaction, while pressure was maintained to 3,380 psig, the reaction temperature and WHSV were variously changed. After the reaction was carried out for 200 hours, 30
5 liters of the solution containing (S)- β -hydroxy- γ -butyrolactone with a selectivity of 84.1% was obtained. In order to recover (S)- β -hydroxy- γ -butyrolactone, the solution was concentrated to remove the solvent, and the acid present therein was removed through esterification using alcohol in the presence of an acid catalyst. Subsequently, methyl-di-hydroxy-butyric acid ester as a reaction intermediate was cyclized in the
10 presence of the acid catalyst without any isolation. At this time, the cyclization was carried out with no addition of solvent. The resulting reaction product was then repeatedly extracted 3 times with chloroform. The extracted material was introduced into a glass reactor of 10 liter volume equipped with a vacuum distillator, vacuum distilled at 60 °C under 100 mbar to remove the solvent, and then concentrated. Using
15 a thin film evaporator, the concentrated product was further vacuum distilled at 100-120 °C under 0.6-1.7 torr. As a result, (S)- β -hydroxy- γ -butyrolactone having an isolation yield of 65%, purity of 98.00%, and optical purity of 99.32% was obtained.

INDUSTRIAL APPLICABILITY

As described above, according to the production process of the present
20 invention, chemically pure (S)- β -hydroxy- γ -butyrolactone having desired optical activity can be obtained by hydrogenating the carboxylic acid ester derivative in the presence of the catalyst system comprising metal-impregnated support. Therefore, the inventive process is advantageous in light of higher purity, higher optical purity and

higher yield of the desired product, and relatively simpler and environmentally safer process than conventional processes. In addition, the desired product can be produced on a large scale due to increased production efficiency.

5 The present invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

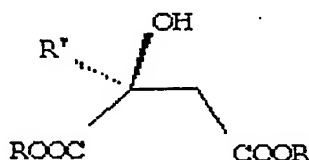
10

CLAIMS

1. A continuous process for the production of chemically pure (S)- β -hydroxy- γ -butyrolactone having desired optical activity, which comprises:

- a) dissolving carboxylic acid ester derivative having the following Formula 2
 5 in solvent at an amount of 2-50 wt%, the solvent being added with an organic or inorganic acid;

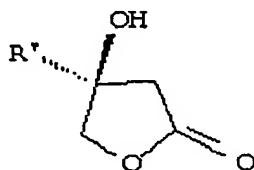
Formula 2



- b) subjecting the carboxylic acid ester derivative solution to hydrogenation at
 10 50-500 °C under a pressure of 15-5,500 psig at weight-hourly-space-velocity of 0.1-10 h⁻¹, in a fixed bed reactor charged with a metal catalyst-impregnated inorganic oxide support, a molar ratio of hydrogen to carboxylic acid ester derivative ranging from 2 to 10; and

- c) recovering (S)- β -hydroxy- γ -butyrolactone having the following Formula 4
 15 from the hydrogenation products,

Formula 4

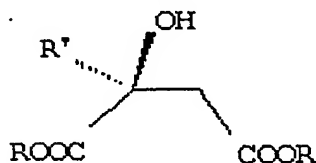


wherein R represents linear or cyclic alkyls, or aryl groups, of from 1 to 10 carbon atoms, and R' represents hydrogen or methyl.

2. A continuous process for the production of chemically pure (S)- β -hydroxy- γ -butyrolactone having desired optical activity, which comprises:

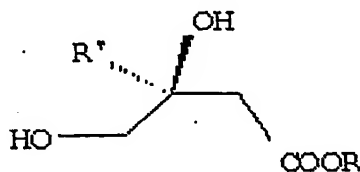
- a) dissolving carboxylic acid ester derivative having the following Formula 2 in solvent at an amount of 2-50 wt%, the solvent being added with an organic or inorganic acid;

Formula 2

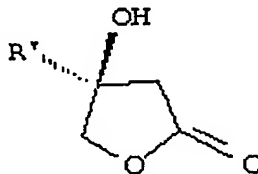


- b) subjecting the carboxylic acid ester derivative solution to hydrogenation at 50-500 °C under a pressure of 15-5,500 psig at weight-hourly-space-velocity of 0.1-10 h⁻¹, in a fixed bed reactor charged with a metal catalyst-impregnated inorganic oxide support to give hydrogenation products containing an intermediate having the following Formula 3 and (S)- β -hydroxy- γ -butyrolactone having the following Formula 4, a molar ratio of hydrogen to carboxylic acid ester derivative ranging from 2 to 10; and

Formula 3



Formula 4



c) subjecting the hydrogenation products to cyclization in the presence of a solid acid catalyst, whereby the intermediate present therein is converted into (S)- β -hydroxy- γ -butyrolactone; and

5 d) recovering said (S)- β -hydroxy- γ -butyrolactone from the resulting products, wherein R represents linear or cyclic alkyls, or aryl groups, of from 1 to 10 carbon atoms, and R' represents hydrogen or methyl.

3. The process as defined in claim 1 or 2, wherein the metal catalyst is selected from the group consisting of nickel (Ni), palladium (Pd), platinum (Pt),
10 rhodium (Rh), iridium (Ir), ruthenium (Ru), osmium (Os), and combinations thereof.

4. The process as defined in claim 1 or 2, wherein the metal catalyst is impregnated at an amount of 0.1-15 wt%.

5. The process as defined in claim 3, wherein the metal catalyst is ruthenium (Ru).

15 6. The process as defined in claim 1 or 2, wherein a degree of dispersion of the metal in the catalyst is adjusted in the range of 2-50%.

7. The process as defined in claim 1 or 2, wherein the hydrogenation step is performed at 60-200 °C.

20 8. The process as defined in claim 1 or 2, wherein the hydrogenation step is performed under a pressure of 1,200-4,500 psig.

9. The process as defined in claim 1 or 2, wherein the hydrogenation step is carried out at weight-hourly-space-velocity of 0.2-6.0 h⁻¹.

10. The process as defined in claim 1 or 2, wherein the organic or inorganic acid additive in the solvent is added at an amount of 0.1-20 wt%, based on the solvent weight.

11. The process as defined in claim 1 or 2, wherein the solvent is selected from the group consisting of methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, dioxane, γ -butyrolactone, tetrahydrofuran, water, and combinations thereof.

12. The process as defined in claim 1 or 2, wherein the acid additive is selected from the group consisting of formic acid, oxalic acid, nitric acid, DL-malic acid, acetic acid, sulfuric acid, phosphoric acid, hydrochloric acid, and combinations thereof.

13. The process as defined in claim 1 or 2, wherein the inorganic oxide support is selected from the group consisting of alumina, silica, silica-alumina, zirconia, titania, zeolite and a molecular sieve.

14. The process as defined in claim 1 or 2, wherein the carboxylic acid ester derivative is obtained by reacting carboxylic acid with a linear, cyclic or aromatic alcohol having 1-10 carbon atoms in the presence of a solid acid catalyst, under conditions of a temperature of 50-150 °C, a pressure of 1.0-300 psig and weight-

hourly-space-velocity of $0.1-10 \text{ h}^{-1}$, in which the alcohol is used at an amount of 2.0-40 equivalents based on the carboxylic acid.

15. The process as defined in claim 14, wherein said carboxylic acid is L-malic acid or L-citramalic acid.

5

16. The process as defined in claim 2, further comprising removing carboxylic acid capable of being present in the hydrogenation products of the step b) through esterification with alcohol in the presence of an acid catalyst prior to the step c).